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Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

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2-(2-Naphthyloxy)acetate derivatives. I. A new class of antiamnesic agents

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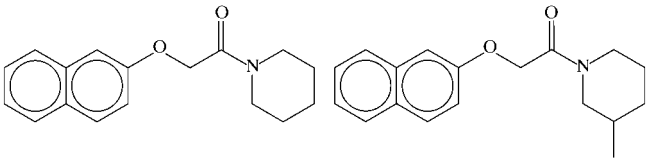
Received 28 May 2003
Accepted 4 June 2003
Online 12 July 2003

The title compounds 1-(2-naphthyloxymethylcarbonyl)piperidine, $C_{17}H_{19}NO_2$, (I), and 3-methyl-1-(2-naphthyloxymethylcarbonyl)piperidine, $C_{18}H_{21}NO_2$, (II), are potential antiamnesics. In (II), the methyl-substituted piperidine ring is disordered over two conformations. The piperidine ring has a chair conformation in both compounds. In (I), the molecules are linked by weak intermolecular C—H···O interactions to give networks represented by $C(4)$, $C(6)$ and $R_4^4(18)$ graph-set motifs, while in (II), weak intermolecular C—H···O interactions generate $R_1^2(5)$, $C(4)$ and $C(7)$ graph-set motifs. The dihedral angle between the naphthalene moiety and the piperidine ring is 33.83 (7)° in (I), while it is 31.78 (11) and 19.38 (19)° for the major and minor conformations, respectively, in (II).

Comment

The conformations of molecules with antiamnesic activity have attracted considerable interest (Amato *et al.*, 1991), and the present structure determinations form part of our research program on biologically active 2-(2-naphthyloxy)acetate derivatives. Increasing effort has been devoted to the search for drugs that can be used for the prevention or treatment of human cognitive disorders (Angelucci *et al.*, 1993). Cognition enhancers are drugs able to facilitate attentional abilities and the acquisition, storage and retrieval of information and to attenuate the impairment of cognitive functions associated with various neurodegenerative states, such as Alzheimer's disease (AD; Gualtieri *et al.*, 2002). Development of cognition enhancers is still a difficult task because of the complexity of brain functions. Hence, several classes of memory enhancers are used, which include acetylcholinesterase inhibitors (Gruzendler & Morris, 2001), acetylcholine precursors, muscarinic receptor agonists and antagonists (Mucke & Castaner, 1998), nicotinic receptor agonists (Vernier *et al.*, 1999), psychostimulants, and nootropics (Parnetti *et al.*, 1997). The brains of people with severe cognition disorder show a consistently depleted cortical and hippocampal cholineacetyl transferase (ChAT) and a decrease in cell density and number in the nucleus basalis of meynert, the major source of cholinergic innervation of the human cortex (Sims *et al.*, 1983; Perry, 1986; Heise, 1987). The cholinergic hypothesis of geriatric dysfunction asserts in essence that the cognitive deficits and memory impairment observed in AD patients are due, at least in part, to deficient cholinergic function (Showell *et al.*, 1991). The cholinergic system has stimulated interest in agents that could enhance central cholinergic transmission. Based on the cholinergic hypothesis, a number of drugs having various mechanistic implications (Moos *et al.*, 1988) have been evaluated against AD. An introspection of the active components of different compounds reveals the correlation of the compounds with the structure of the endogenous neurotransmitter acetylcholine and is considered in postulating the design strategy for the compounds considered here, namely 1-(2-naphthyloxymethylcarbonyl)piperidine, (I), and 3-methyl-1-(2-naphthyloxymethylcarbonyl)piperidine, (II). The improvement of cholinergic transmission is a rational and well documented approach to the improvement of cognition and memory. Therefore, we report here the preparation and X-ray crystal structures of (I) and (II). Full details of the syntheses of these compounds and their biological activity will be published elsewhere (Piplani & Jindal, 2003).



(I) (II)

Views of the molecules of (I) and (II), with the atomic numbering schemes, are depicted in Figs. 1 and 2, respectively. The corresponding bond lengths and angles in (I) and (II) are almost identical. In (I), the central C2—O11—C12—C13—N14 unit is effectively planar, and the overall molecular conformation can be defined in terms of the torsion angles involving this unit. In (II), atoms N14*A* and N14*B* deviate by −0.171 (4) and 0.268 (9) Å, respectively, from the mean plane of the central fragment. The central unit is almost coplanar with the naphthalene ring in both compounds and adopts an antiperiplanar conformation (Table 3). The piperidine ring in (I) adopts a chair conformation, as shown by the puckering parameters for atom sequence N14—C15—C19 [Q = 0.566 (3) Å, q_2 = 0.017 (3) Å, q_3 = −0.566 (3) Å, θ = 177.7 (3)° and φ_2 = 40 (9)°; Cremer & Pople, 1975].

The 3-methylpiperidine ring in (II) is disordered over two conformations, with the major conformation existing in 69.5 (5)% of the molecules. As seen from the puckering parameters, each disordered component has a chair conformation [Q = 0.547 (5) Å, q_2 = 0.012 (5) Å, q_3 = 0.547 (5) Å, θ = 1.7 (5)° and φ_2 = 211 (22)° for atom sequence N14*A*—C15*A*—C19*A* of the major conformation, while the corresponding values are Q = 0.539 (10) Å, q_2 = 0.027 (10) Å, q_3 = −0.538 (10) Å, θ = 176.9 (11)° and φ_2 = 283 (23)° for the

† Deceased.

  DOI: 10.1107/S0108270103012332

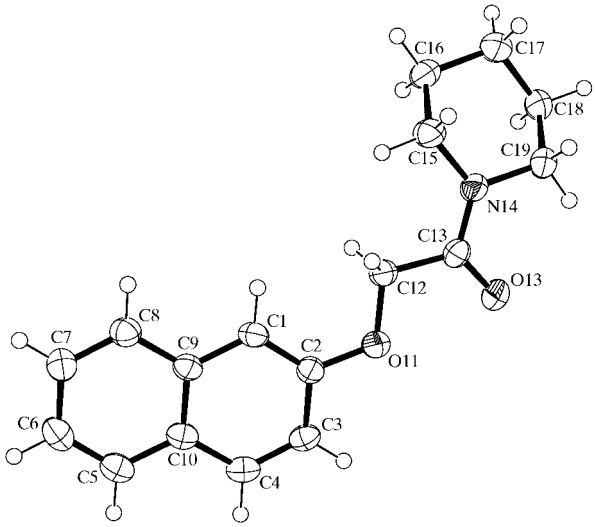


Figure 1
A view of the molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are represented by circles of arbitrary radii.

minor conformation]. The angle between the mean planes through the naphthalene moiety and the piperidine ring is 33.83 (7)° in (I), whereas it is 31.78 (11) and 19.38 (19)° for the major and minor conformations, respectively, in (II).

The exocyclic C1—C2—O11, C13—N14—C15, C13—N14*A*—C15*A* and C13—N14*B*—C15*B* bond angles deviate significantly from the normal value of 120° (Tables 1 and 3), and this deviation may be due to steric repulsion [H1···H121 = 2.28 Å (2.36 Å), H1···H122 = 2.28 Å (2.09 Å), H121···H152 = 2.12 Å (H121···H151 = 2.24 Å and H121···H154 = 2.03 Å) and H122···H152 = 2.26 Å (H122···H151 = 2.14 Å and H122···H154 = 2.45 Å); the values in parentheses apply to (II)].

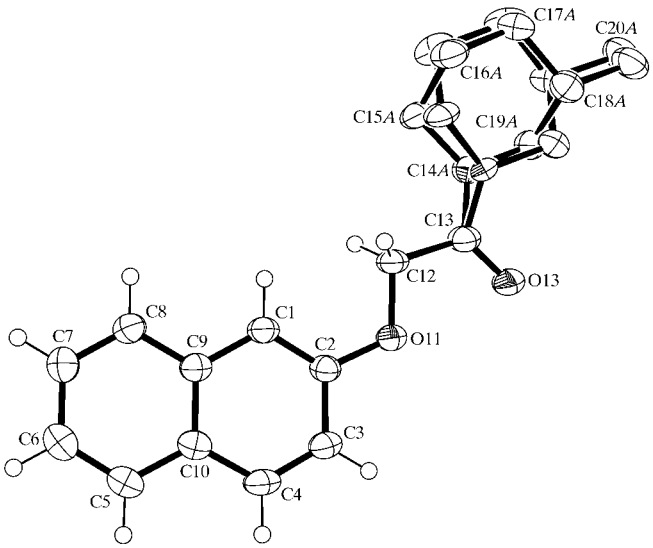


Figure 2
A view of the molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level. For clarity, all H atoms of the disordered methyl-substituted piperidine ring have been omitted. The other H atoms are represented by circles of arbitrary radii.

As can be seen from Table 2, in (I), atom C12 acts as a donor in a weak intermolecular C—H···O interaction with the carbonyl O13 atom of an adjacent molecule. This interaction produces a continuous chain that runs parallel to the *a* axis and has a graph-set motif of *C*(4) (Bernstein *et al.*, 1995). Atom C15 participates in a weak intermolecular C—H···O interaction with atom O11 of an adjacent molecule. This interaction links the molecules into another continuous chain, which runs parallel to the *c* axis and has a graph-set motif of *C*(6). These two chains combine to form an $R_4^4(18)$ ring.

In (II), atom C1 is involved in a weak intermolecular bifurcated C—H···O interaction with atoms O11 and O13 of the molecule at $(-y+\frac{1}{2}, x, z-\frac{1}{4})$ (Table 4), which leads to an $R_1^2(5)$ motif. Taken individually, these interactions link molecules into a different type of continuous chain, which runs parallel to the *c* axis and has graph-set motifs of *C*(4) and *C*(7) for the interactions involving atoms O11 and O13, respectively.

Experimental

For the preparation of (I), methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with piperidine and the oily product was treated with ice-cold water. The resulting precipitate was filtered off, dried and crystallized from petroleum ether to afford crystals of (I) (yield 0.524 g, 84.14%; m.p. 353–357 K). For the preparation of (II), methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with 3-pipecoline and the oily product was treated with water. The resulting precipitate was filtered off, dried and crystallized from acetone to afford crystals of (II) (yield 0.498 g, 76.01%; m.p. 363–365 K).

Compound (I)

Crystal data

$C_{17}H_{19}NO_2$
M_r = 269.33
Orthorhombic, $Pna2_1$
a = 9.8769 (1) Å
b = 24.8789 (3) Å
c = 5.7335 (1) Å
V = 1408.87 (3) Å^3
Z = 4
D_x = 1.270 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1495 reflections
θ = 2.0–25.0°
μ = 0.08 mm^{-1}
T = 160 (2) K
Plate, colourless
0.28 × 0.13 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
φ scans, and ω scans with κ offsets
25 142 measured reflections
1373 independent reflections
1166 reflections with $I > 2\sigma(I)$
R_{int} = 0.056
θ_{max} = 25.0°
$h = -11 \rightarrow 11$
$k = -29 \rightarrow 29$
$l = -6 \rightarrow 6$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.090
S = 1.08
1372 reflections
182 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0597P)^2 + 0.0272P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.016 (4)

Table 1
Selected geometric parameters (°) for (I).

C13—N14—C15	126.38 (19)	O13—C13—N14	123.6 (2)
C1—C2—O11	125.6 (2)		
C2—O11—C12—C13	−174.30 (18)	O11—C12—C13—N14	−174.49 (18)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
C12—H122···O13^{i}	0.99	2.36	3.345 (3)	174
C15—H151···O11^{ii}	0.99	2.53	3.374 (3)	142

Symmetry codes: (i) $x-\frac{1}{2},\frac{1}{2}-y,z$; (ii) $x,y,z-1$.

Compound (II)

Crystal data

$C_{18}H_{21}NO_2$
$M_r = 283.36$
Tetragonal, $I4_1cd$
$a = 20.9438$ (4) Å
$c = 13.9169$ (2) Å
$V = 6104.55$ (19) Å^3
$Z = 16$
$D_x = 1.233$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1554 reflections
$\theta = 2.0$–$25.0°$
$\mu = 0.08$ mm^{-1}
$T = 160$ (2) K
Prism, colourless
0.25 × 0.18 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
ω scans with κ offsets
19 971 measured reflections
1414 independent reflections
1273 reflections with $I > 2\sigma(I)$
$R_{int} = 0.052$
$\theta_{max} = 25.0°$
$h = 0 \rightarrow 24$
$k = 0 \rightarrow 17$
$l = -16 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.085$
$S = 1.06$
1414 reflections
257 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0591P)^2 + 0.4966P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.11$ e Å^{-3}
$\Delta\rho_{min} = -0.13$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0041 (7)

Table 3
Selected geometric parameters (°) for (II).

C1—C2—O11	124.26 (18)	C13—N14*A*—C15*A*	126.5 (3)
O13—C13—N14*A*	123.6 (2)	C13—N14*B*—C15*B*	124.6 (6)
O13—C13—N14*B*	119.4 (4)		
C2—O11—C12—C13	−172.85 (17)	O11—C12—C13—N14*B*	−162.8 (5)
O11—C12—C13—N14*A*	168.5 (3)		

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C1—H1···O11^{iii}	0.95	2.57	3.386 (2)	145
C1—H1···O13^{iii}	0.95	2.40	3.241 (2)	147

Symmetry code: (iii) $\frac{1}{2}-y,x,z-\frac{1}{4}$.

For (I), all H atoms were placed in idealized positions (C—H = 0.95–0.99 Å) and constrained to ride on their parent atoms, with U_{iso}(H) values of $1.2U_{eq}$(C). Although the molecule is achiral, the structure possesses a polar axis. Because of the absence of any significant anomalous scatterers in the compound, attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 1005 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of 1.8 (14) for this parameter. Therefore, the absolute direction of the polar axis was assigned arbitrarily and the Friedel pairs were merged before the final refinement. Reflection 110 was partially obscured by the beam stop and was omitted. For (II), the methyl-substituted six-membered ring is disordered over two conformations. Two sets of positions were defined for piperidine atoms N14/C15–C19 and for the atoms of the C20 methyl group. Constrained refinement of the site-occupation factors for these groups led to a value of 0.695 (5) for the major conformation. Similarity restraints were applied to all 1,2 and 1,3 distances involving disordered atoms, so as to maintain similar geometry about the chemically equivalent atoms. Methyl H atoms were constrained to an ideal geometry (C—H = 0.98 Å), with U_{iso}(H) values of $1.5U_{eq}$(C), but were allowed to rotate freely about the C—C bonds. All remaining H atoms were placed in idealized positions (C—H = 0.95–1.00 Å) and constrained to ride on their parent atoms, with U_{iso}(H) values of $1.2U_{eq}$(C). Again, although the molecule is achiral, the structure possesses a polar axis. Because of the absence of any significant anomalous scatterers in the compound, attempts to confirm the absolute structure by refinement of the Flack (1983) parameter in the presence of 1163 sets of Friedel equivalents led to an inconclusive value (Flack & Bernardinelli, 2000) of 0.9 (11) for this parameter. Therefore, the absolute direction of the polar axis was assigned arbitrarily and the Friedel pairs were merged before the final refinement.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN* and *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 2003).

ST thanks the X-ray Crystallography Facility, Institute of Organic Chemistry, University of Zurich, Switzerland, for providing access to the facility during his visit in August 2002.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1646). Services for accessing these data are described at the back of the journal.

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